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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **PP#6E04667. PYRIDATE.** Tolerance on/in Garbanzo Beans (Chick Peas).

DP Barcode: D223398 Caswell #: 716A
PRAT Case #:287340 Chemical #: 128834
40 CFR 180.462 Class: Herbicide

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I. INTRODUCTION

The petitioner, Interregional Research Project No. 4 (IR-4), on behalf of the Agricultural Experiment Station of Washington, proposes the establishment of a tolerance for the combined residues of the herbicide pyridate [O-(6-chloro-3-phenyl-4-pyridazinyl)-S-octyl-carbonothioate], in or on the raw agricultural commodity (RAC) garbanzo beans (also known as chick peas) at 0.1 ppm.

Permanent tolerances are established for residues of pyridate [O-(6-chloro-3-phenyl-4-pyridazinyl)-S-octyl-carbonothioate], the metabolite 6-chloro-3-phenyl-pyridazine-4-ol and conjugates of 6-chloro-3-phenyl-pyridazine-4-ol, expressed as pyridate (40 CFR 180.462) on cabbage, corn (forage, fodder, grain, silage), and peanuts (hulls, nutmeat) at 0.03 ppm.

There are no food or feed additive tolerances. No tolerances have been established on animal commodities. Pyridate is not registered for outdoor residential or greenhouse uses.

II. EXECUTIVE SUMMARY

HED has reviewed field trial data submitted by the petitioner IR-4, on behalf of the Agricultural Experiment Station of Washington to support establishment of a tolerance for pyridate on/in garbanzo beans (chick peas). Pyridate was reviewed by the Hazard I.D. Assessment Review Committee (10/21/97) to evaluate the toxicology database and to address sensitivity of infants and children from exposure to this chemical. The

Committee also reassessed doses and endpoints for acute dietary, chronic dietary as well as occupational and residential risk assessments. The following dose/endpoint selections and risk assessment determinations were made:

- Acute dietary, NOEL= 20 mg/kg/day. Risk assessment is required.
- Chronic dietary, RfD = 0.11 mg/kg/day. (NOEL = 10.8 mg/kg/day; Uncertainty Factor = 100)
- Short- and intermediate-term dermal, NOEL = 20 mg/kg/day. Risk assessment required.
- Long-term, NOEL = 10.8 mg/kg/day. Risk assessment is required.
- Inhalation exposure, short-, intermediate, and long-term same as above. Risk assessment required.
- No additional factors required to address sensitivity of infants and children were required.
- No developmental neurotoxicity study was required.
- No data gaps.

Based on the Committee's recommendations, acute and chronic dietary exposure (food + water) were performed and were found not to exceed HED's level of concern. Similarly, occupational exposure estimates for pyridate were also found not to exceed HED's level of concern. Because pyridate has no residential uses, residential exposure was not performed. The data submitted by the petitioner indicate that residues will not exceed the proposed tolerance level. **Provided that the Section B/label is revised to prohibit the use of adjuvants, HED recommends in favor of the establishment of the proposed tolerance for the combined residues (as expressed under 40 CFR 180.462) of pyridate in or on garbanzo beans at 0.1 ppm. The Section B/label should be revised regarding adjuvants to read as follows: "Adjuvants (non-ionic surfactants, crop oil or liquid fertilizer) are prohibited from use with TOUGH 3.75 EC when used on garbanzo beans."**

III. SCIENCE ASSESSMENT

A. PHYSICAL AND CHEMICAL PROPERTIES ASSESSMENT

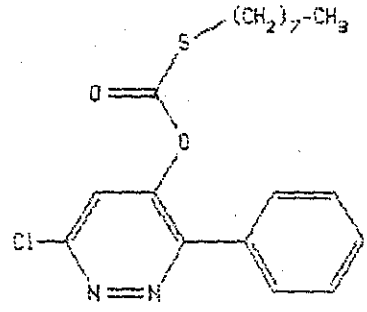
The manufacturing process and other product chemistry data required for registration have been previously reviewed and found adequate (see PP#8F3603, 2/6/91). Technical pyridate contains 91% ai; impurities are not expected to pose a residue problem.

The formulation proposed for use on garbanzo beans is Tough 3.75EC.

1. Description of Chemical

Pyridate is a herbicide used for post emergence control of several weed species in garbanzo bean production.

Figure A. Pyridate



Molecular Formula: $C_{19}H_{23}ClN_2O_2S$
Molecular Weight: 378.92
Caswell No.: 716A

CAS Registry No.: 55512-33-9
Shaughnessy/Chemical No.: 128834

Table 1. Description of Pyridate

IUPAC name	6-chloro-3-phenylpyridazin-4-yl S-octyl thiocarbonate
Color	White-crystalline solid when pure; technical is a brown, oily liquid
Density	1.555 g/ml at 20°C (technical)
Melting Point	27°C
Boiling Point	>220°C at 0.105 mm Hg
Vapor Pressure	1.01×10^{-7} mm Hg at 20°C

Stability	Not degraded by UV light
Solubility	water: 1.5 mg/L at 20°C acetone: >10g/100 ml at 20°C benzene: >10 g/100 ml at 20°C methanol: >12 g/100 ml at 20°C toluene: >10 g/100 ml at 20°C
pK_a	none
Octanol/Water Partition Coefficient	K_{ow} = > 1000

B. HUMAN RISK ASSESSMENT

1. Hazard Assessment

The toxicological data base on pyridate is adequate and will support registration (HAZARD ID Committee, 11/4/97).

a. Acute Toxicity

The following table summarizes acute toxicity values and categories for pyridate:

Table 2. Acute Toxicity of Pyridate (Technical)

GDLN	STUDY	RESULTS
81-1	Acute Oral Toxicity in Rats Accession # 072340 Report # RCC 036990 Date: 10/84 Acceptable	LD_{50}: 5993 mg/kg (males) LD_{50}: 3544 mg/kg (females) TOXICITY CATEGORY: III
81-2	Acute Dermal Toxicity in Rabbits Accession # 073280 Report # RCC 037001 Date: 10/84 Acceptable	LD_{50}: > 2000 mg/kg TOXICITY CATEGORY: III

81-3	Acute Inhalation Toxicity in Rats Accession # 073280 Report # RCC 016255 Date: 5/83 Acceptable	LC_{50}: > 4.37 mg/L (four hour exposure) TOXICITY CATEGORY: IV
81-4	Primary Eye Irritation in Rabbits Accession # 072340 Report # Hunt. 6528 Acceptable	Primary Irritation Score: Nonirritant TOXICITY CATEGORY: IV
81-5	Primary Dermal Irritation in Rabbits Accession #072340 Report # HUNT. 6527 Date: 9/76 Acceptable	Primary Irritation Score: 3.3 TOXICITY CATEGORY: III slightly irritating to the skin under conditions of test
81-6	Dermal Sensitization in Guinea Pigs MRID #403571-02 Report #87R-035 Date: 6/25/87 Acceptable	Magnusson & Kligman method Positive sensitizing reaction

b. Subchronic Toxicity

The following table summarizes subchronic toxicity values and categories for pyridate:

Table 3. Subchronic Toxicity of Pyridate (Technical)

GDLN	STUDY	RESULTS
82-1(a)	Subchronic Feeding in Rats (13 weeks) MRID #: 40157401 Report #043-005 Date: 4/87 Core Grade: Guideline	NOEL: 62.5 mg/kg/day LOEL: 177 mg/kg/day Effects: hypoactivity and salivation in both sexes

82-1(b)	Subchronic Feeding in Dogs (13 weeks) MRID # 40101604 Report #043-002 Date: 2/87 Core Grade: Guideline	NOEL: 20 mg/kg/day LOEL: 60 mg/kg/day Effects: Emesis and ataxia in both sexes at LOEL [60 mg/kg/day]. Severe neurotoxicity and death at 200 mg/kg/day [HDT]
82-2	21-day dermal in rats MRID #: 40980401 Report #437242 Date: 10/3/88 Guideline	NOEL for systemic effects: >1000 mg/kg/day [limit dose]. LOEL for systemic effects was not established in this study Effects: No systemic toxicity at any dose tested

c. Chronic Toxicity

The following table summarizes chronic toxicity values and categories for Pyridate:

Table 4. Chronic Toxicity of Pyridate (Technical)

GDLN	STUDY	RESULTS
83-1 b	Chronic feeding study in dogs MRID # 41093901 Report #2495-100 Date: 5/2/89 Core Grade: Minimum	NOEL: 20 mg/kg/day LOEL: 100 mg/kg/day Methods & Effects: 91.5% material fed by capsule to 5 dogs/group/dose at levels of 0, 5/30, 20/100, or 60/150 for one year. LOEL: 100 mg/kg/day; based on excessive salivation, ataxia, mydriasis, dyspnea, tremors, increased respiration and prostration. NOEL: 20 mg/kg/day

d. Carcinogenicity

The following tables summarize carcinogenicity values and categories for pyridate:

Table 5. Carcinogenicity of Pyridate (Technical)		
GDLN	STUDY	RESULTS
83-2(a)	Oncogenicity study in mice MRID #42168001 Report #91-603 Date: 11/7/91 Core Grade: Minimum	NOEL and LOEL: could not be established due to decreased weight gain in both sexes at all doses Methods & Effects: 90.4% test material given to male and female B6C3F1 mice in diet for 18 months at 0, 400, 800, 1600 ppm or 7000 ppm (0, 47.7, 97.1, 169.5, or 882.6 mg/kg/day for males; 0, 54.5, 114.6, 204.3, or 1044.6 mg/kg/day for females. No statistically significant increase in tumor incidence relative to controls were observed in either sex at any dose, including the limit dose [7000 ppm].
83-5	Chronic Feeding/ Oncogenicity study in rats MRID #00072342, 00072343, 00072350 Report #171 & 172 Date: 6/83 Core Grade: Minimum	NOEL: 10.8 mg/kg/day LOEL: 67.5 mg/kg/day Methods & Effects: Technical (90.3%) administered to male and female SPF rats in diet for 24 months at 0, 43, 215 & 1350 ppm (0, 2.2, 10.8 or 67.5 mg/kg/day). Decrease in body weight in males at 67.5 mg/kg/day was basis of LOEL. NOEL is 10.8 mg/kg/day.

e. Developmental Toxicity

The following table summarizes developmental toxicity values and categories for pyridate:

Table 6. Developmental Toxicity of Pyridate (Technical)		
GDLN	STUDY	RESULTS
83-3	Developmental Study in Rabbits MRID# 40463201 Report #512-001 Date: 12/10/87 Core Grade Guideline	Maternal NOEL: 300 mg/kg/day Maternal LOEL: 600 mg/kg/day Methods & Effects: technical 89.5% administered to female New Zealand White rabbits 0 (water control), 150.0, 300.0 or 600.0 mg/kg/day a.i. by oral gavage (5 ml/kg b.w.) on days 7-19 of gestation. LOEL was based on reduced body weight and body weight gain during the dosing period. Developmental NOEL:>600 mg/kg/day Developmental LOEL: not established

83-3	Developmental Study in Rats MRID 00262546 Report # 055934 Date: 2/7/86 Core Grade Guideline	Maternal NOEL: 165 mg/kg/day Maternal LOEL: 400 mg/kg/day Methods & Effects: Technical (92%) administered to Wistar/HAN rats at 0, 55, 165, 400, or 495 mg/kg/day by oral gavage from gestation days 6-15, inclusive. Mortality and decreased body weight at LOEL of 400 mg/kg/day and higher. Developmental NOEL: 165 mg/kg/day Developmental LOEL: 400 mg/kg/day Effects: Increased incidences of missing or unossified sternebrae and decreased fetal body weight at 400 mg/kg/day and above.

f. Reproductive Toxicity

The following table summarizes reproductive toxicity values and categories for pyridate:

Table 7. Reproductive Toxicity of Pyridate (Technical)

GDLN	STUDY	RESULTS
83-4	3 - Generation Reproduction Toxicity in Rats MRID 00072347 Report #B80-0696 Date: 8/82 Core Grade Guideline	Systemic NOEL: 216 ppm (10.8 mg/kg/day) Systemic LOEL: 1350 ppm (67.5 mg/kg/day) Methods & Effects: Technical (90.3% pure administered to male and female SPF rats at 0, 43, 216 or 1350 ppm in diet (0, 2.2, 10.8 or 67.5 mg/kg/day). LOEL for reproduction [pups] and systemic parental effects based on decreased body weight. Reproductive NOEL: 216 ppm (10.8 mg/kg/day) Reproductive LOEL: 1350 ppm (67.5 mg/kg/day) Effects: Decreased pup body weight during lactation

g. Mutagenicity

The following tables summarize mutagenicity values and categories for pyridate:

Table 8. Mutagenicity of Pyridate (Technical)		
GDLN	STUDY	RESULTS
84-2(a)	Gene Mutation Assay (Ames Test) MRID 40101602 Report #:E-9550 Date: 9/19/86 Acceptable	No appreciable increase in the reversion to histidine protrophy of 4 S. typhimurium strains at 1 to 10,000 ug/plate with & without S-9 activation.
84-2(a)	Gene Mutation Assay Mammalian Cells MRID 40186502 Report #EO9550 Date: 1/87 Acceptable	Nonclastogenic in Chinese Hamster Ovary Cells with and without metabolic activation up to 250 ug/ml.
84-2(b)	Structural Chromosomal Aberration Assay In vivo cytogenetics MRID 00072348 Report #22021-01 Date: 8/80 Acceptable	Nonclastogenic in chromosomal aberrations in bone marrow cells sampled over the entire mitotic cycle at doses from 0.073 to 0.725 grams/ml.
84-2(b)	Structural Chromosomal Aberration Assay In vivo cytogenetics MRID 40116401 Report #263.215016 Date: 12/86 Acceptable	Did not induce chromosomal aberrations [nonclastogenic] with & without metabolic activation under the conditions of the study up to 4 grams/kg.
84-2©	Other Genotoxicity Assays (Unscheduled DNA Synthesis) MRID 40857001, 40982601 Report #T8186.381 Date: 8/29/88 Acceptable	Did not induce an increase in unscheduled DNA synthesis up to toxic dose. 0.1-1000 ug/ml tested.

h. Metabolism (rat)

The following table summarizes rat metabolism values and categories for pyridate:

Table 9. Rat Metabolism of Pyridate (Technical)

GDLN	STUDY	RESULTS
85-1	Metabolism MRID 00072349 Report #A0070 Date: 9/79 Acceptable	Rapidly absorbed and excreted. Greater than 95% was eliminated by 24 hrs. Extensively metabolized prior to excretion. Metabolic patterns similar for both sexes.
85-1	Metabolism MRID 00072349 Report #A0071 Date: 9/79 Acceptable	Completely and rapidly absorbed. Extensively metabolized and rapidly and essentially completely excreted. Elimination of label from single dose of 5.45 mg/rat of C14-pyridate.
85-1	Metabolism MRID 00072349 Report #2946 Date: 7/78 Acceptable	Multiple oral doses [5 mg/rat/day for 10, 15, or 20 days] results in bioaccumulation in liver, spleen and fat. Clearance from all tissues was slower after repeated exposure. Female rats eliminated radioactivity slower than males.

I. Neurotoxicity

Neurotoxicity was observed in the 90 day rat and dog studies and the one-year dog study. Clinical signs indicative of neurotoxicity characterized as ataxia and emesis were observed within 1-3 hours post-dosing on the first day and persisted for duration of study.

j. Other Toxicological Considerations

The HAZID Committee (10/21/97) determined that a developmental neurotoxicity assessment was not required based on the following weight-of-evidence:

- Dogs appear to be a more sensitive species with clinical signs indicative of neurotoxicity (emesis, ataxia, opisthotonos and hyperactivity) occurring only at high doses.
- In a range-finding study in dogs,. no treatment-related effects were seen at doses up to and including 33 mg/kg/day; clinical effects with neurological sings were seen only at doses of 100-400 mg/kg/day. In the 90-day study, clinical signs were seen at 200 mg/kg/day.

- In the subchronic toxicity study with dogs, brain cholinesterase activity was not affected. Plasma and red blood cell cholinesterase activity was inhibited only at 500/600 mg/kg/day dose.

- In a subchronic study in rats, clinical signs were seen only at doses of 500 or 500/600 mg/kg/day indicating that rats are not the most sensitive species (i.e., clinical signs occur at doses even higher than that in dogs).

- No evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats, or rabbits, at maternally toxic oral doses up to 400 and 600 mg/kg/day, respectively.

- There were no effects on absolute brain weight in the subchronic or chronic studies in which this was measured.

- The doses (i.e., 10.8 mg/kg/day for RfD and 20.0 mg/kg/day for Acute and Chronic dietary/non-dietary exposure) used for regulations are protective of the neurotoxic effects that occur at higher dose.

Pyridate has a complete database and no other toxicological concerns have been identified in the evaluated studies.

2. Dose/Response Assessment

a. Reference Dose (RfD) for Pyridate

Groups of SPF rats (15/sex/dose) were feds diets containing pyridate at 0, 43, 216 or 1350 ppm (0, 2.2, 10.8 or 67.5 mg/kg/day, respectively) for 104 weeks. The NOEL was 216 ppm (10.8 mg/kg/day) and the LOEL was 1350 ppm (67.5 mg/kg/day) based on decreased body weight gain in males. An uncertainty factor (UF) of 100 was applied to account for inter (10 x)-and intra-(10 x) species variation. The **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **was removed, since there was no special sensitivity for infants and children.** For chronic dietary risk assessment, **a UF of 100 is adequate** for the protection of this subpopulation from exposure to pyridate. **Consequently, the RfD is 0.11 mg/kg/day.**

b. Carcinogenic Classification

Pyridate is classified as Category E: not carcinogenic in two acceptable animal studies.

c. Developmental and Reproductive Toxicity

The oral rat and rabbit developmental studies and the oral rat reproduction study demonstrated no indication of increased sensitivity of rats or rabbits to *in utero and postnatal* exposure to pyridate.

In a prenatal developmental toxicity study in Wistar/HAN rats, pyridate in carboxymethylcellulose was administered at doses of 0, 55, 165, or 400 mg/kg/day by gavage on gestation days 6-15. For maternal toxicity, the NOEL was 165 mg/kg/day and the LOEL was 400 mg/kg/day based on mortality, significant decrease in mean body weight and food consumption as well as clinical signs (ventral body position, dyspnea,

sedation, and loss of reaction to external stimuli). The developmental NOEL was 165 mg/kg/day and the developmental LOEL was 400 mg/kg/day, based on increased incidences of missing and/or unossified sternebrae and dose-related decrease in mean fetal body weight. ***(MRID 00262546)***.

A prenatal developmental toxicity study was conducted in pregnant New Zealand white rabbits, in which pyridate (neat) was administered by gavage at doses of 0, 150, 300 or 600 mg/kg/day on gestation days 7-19. For maternal toxicity, the NOEL was 300 mg/kg/day and the LOEL was 600 mg/kg/day, based on decreased body weight and body weight gain, decreased food consumption, increased incidence of dried feces, and increased abortions. For developmental toxicity the NOEL $\geq$ 600 mg/kg/day (HDT); a LOEL was not established (MRID 40463201)..

In a three-generation reproduction study, Sprague-Dawley rats received diets containing pyridate at doses of 0, 43,216 or 1350 ppm (0, 2.2, 10.8 or 67.5 mg/kg/day, respectively). Each generation of rats was mated to produce two litters. The parental systemic NOEL was 216 ppm (10.8 mg/kg/day) and the LOEL was 1350 ppm (67.5 mg/kg/day) based on depression of maternal body weight gain. The NOEL for offspring was 216 ppm (10.8 mg/kg/day) and the LOEL was 1350 ppm (67.5 mg/kg/day) based on decreased pup weight gains (at postnatal and day 14 and 21 in the first litters for both generations ***(MRID No.00072347)***.

d. Determination of Safety for Infants and Children

The oral perinatal and prenatal data demonstrated no indication of increased sensitivity of rats or rabbits to *in utero and postnatal* exposure to Pyridate. The **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **was removed by the HAZARD ID Committee.**

e. Other Toxicological Endpoints

I. Acute Dietary (1 day)

Groups of beagle dogs (4/sex/dose) received gelatin capsules containing pyridate at doses of 0, 20, 60 or 200 mg/kg/day for 90 days. The NOEL was 20 mg/kg/day and the LOEL was 60 mg/kg/day based on ataxia and emesis observed within 1-3 hours dosing beginning on the first day. All dogs at 200 mg/kg/day exhibited severe emesis and severe ataxia 1 to 3 hours post dosing and signs of opisthotonos, nystagmus and mydriasis also occurred within 3 hours after dosing. Although animals returned to their normal condition prior to dosing the next day, for the first 20 days some signs of toxicity persisted until dosing. Animals at 60 mg/kg/day exhibited fewer and less severe signs of toxicity than dogs at 200 mg/kg/day. **The acute dietary endpoint selected for risk assessment was the NOEL of 20 mg/kg/day based on ataxia and emesis at 60 mg/kg/day**.

Clinical signs indicative of neurotoxicity characterized as ataxia and emesis were observed within 1-3 hours post-dosing on the first day and persisted for duration of study.

Clinical signs indicative of neurotoxicity observed in dogs is supported by similar neurotoxic clinical signs in rats. In a 90-day feeding study, hypoactivity was seen one hour post dosing, reaching a peak on weeks 3, 4 and 5 in rats fed diets containing pyridate at 500 or 500/600 mg/kg/day for 90 days.

ii. Dermal absorption

Dermal Absorption - A dermal absorption study was not available for evaluation. Therefore, the Committee estimated a dermal absorption rate of 20% percent based on the interpretation of data from oral and dermal studies in rats.

In the oral developmental toxicity study in rat, the maternal NOEL was 165 mg/kg/day based on mortality, significantly decreased mean body weight and food consumption and clinical signs.

In the 21-day dermal toxicity study in rats, no dermal or systemic toxicity was observed at the Limit-Dose of 1000 mg/kg/day.

In extrapolating from oral to dermal route, the Committee made the following assumptions: 1) that the toxicity seen via the oral route is due to direct transport of pyridate from the absorption site to the target organs and 2) that metabolism following oral and dermal routes are similar. Under these assumption, no more than 16% (oral dose of 165 mg/kg/day ÷ dermal dose 1000 mg/kg/day x 100) of pyridate applied to the rat skin is absorbed without effects.

The Hazard ID Committee, however, due to the uncertainties in extrapolating from the oral to dermal route from the available data, decided to use a conservative dermal absorption value of 20% in the absence of definitive dermal absorption data.

iii. Short (1 day to 7 days) and Intermediate (1 week to several months) Term Occupational and Residential Exposure

Groups of beagle dogs (4/sex/dose) *[MRID # 40101604]* received gelatin capsules containing pyridate at doses of 0, 20, 60 or 200 mg/kg/day for 90 days. The NOEL was 20 mg/kg/day and the LOEL was 60 mg/kg/day based on ataxia and emesis observed within 1-3 hours dosing beginning on the first day. All dogs at 200 mg/kg/day exhibited severe emesis and severe ataxia 1 to 3 hours post dosing and signs of opisthotonos, nystagmus and mydriasis also occurred within 3 hours after dosing. Although animals returned to their normal condition prior to dosing the next day, for the first 20 days some signs of toxicity persisted until dosing. Animals at 60 mg/kg/day exhibited fewer and less severe signs of toxicity than dogs at 200 mg/kg/day. **The short and intermediate occupational and residential endpoint selected for risk assessment was the NOEL of 20 mg/kg/day based on ataxia and emesis at 60 mg/kg/day. Dogs were selected for short and intermediate term endpoints because the neurotoxic effects were seen on the first day and persisted for the duration of the 90 day study.**

Clinical signs indicative of neurotoxicity characterized as ataxia and emesis were observed within 1-3 hours post-dosing on the first day and persisted for duration of study.

Clinical signs indicative of neurotoxicity observed in dogs is supported by similar neurotoxic clinical signs in rats. In a 90-day feeding study, hypoactivity was seen one hour post dosing, reaching a peak on weeks 3, 4 and 5 in rats fed diets containing pyridate at 500 or 500/600 mg/kg/day for 90 days.

Although a 21-day dermal toxicity study in rats was available and no dermal or systemic toxicity was demonstrated in that study at the Limit-Dose, an oral dose from the 90-day dog study was selected because 1) dogs were shown to be the sensitive species for pyridate-induced neurotoxic effects and 2) the effects seen on the first day persisted for the duration of study.

Since an oral dose was selected, **a dermal absorption rate no more than 20% should be used for risk assessments.**

iv. Chronic Occupational and Residential (Non-Cancer)

Groups of SPF rats (15/sex/dose) were feds diets containing pyridate at 0, 43, 216 or 1350 ppm (0, 2.2, 10.8 or 67.5 mg/kg/day, respectively) for 104 weeks. The NOEL was 216 ppm (10.8 mg/kg/day) and the LOEL was 1350 ppm (67.5 mg/kg/day) based on decreased body weight gain in males. **The NOEL of 10.8 mg/kg/day based on decreased body weight gain in male rats at 67.5 mg/kg/day (LOEL) was selected by the HAZARD ID Committee for chronic occupational and residential risk assessment.**

The Committee noted that the dose of 10.8 mg/kg/day established in the above study is supported by the Parental Systemic Toxicity NOEL and LOEL established in the Two-Generation reproduction study in rats. In that study the NOEL was 10.8 mg/kg/day and the LOEL was 67.5 mg/kg/day based on decreased pup weight gain (at post natal day 14 and 21 in the first litters of both generations).

Since an oral dose was identified, a DA [dermal absorption] factor of no more than 20% should be used for risk assessments. The 20% dermal absorption was estimated based on the comparative oral and dermal NOELs established in the same species. This dose and endpoint were also used for chronic dietary risk assessment.

v. Inhalation Exposure

In general, a risk assessment for inhalation route is not necessary for pesticides placed in Toxicity Category IV (i.e., low toxicity concern). Pyridate, based on the LC_{50} value of 4.37 mg/L is placed in Toxicity Category IV. However, because of the potential for exposure via this route, a risk assessment may be required.

Since only an acute inhalation toxicity study was available, **the Committee recommended the use of oral NOELs for the inhalation exposure risk assessments.**

The 90-day dog feeding study was chosen for short-and intermediate-term inhalation exposure [NOEL = 20 mg/kg/day] and the chronic toxicity/carcinogenicity rat feeding study was chosen for long-term inhalation exposure [NOEL = 10.8 mg/kg/day].

The Committee selected NOELs for these risk assessments because of the: 1) lack of appropriate inhalation studies and 2) potential for exposure via this route.

The doses identified for inhalation risk assessments are from oral studies (i.e., use of oral NOEL). Therefore, risk assessment should be as follows:

(I) The inhalation exposure component (i.e., mg/L) using a 100 % inhalation absorption rate (default value) should be converted to an equivalent oral dose (mg/kg/day).

(ii) The dermal exposure component (i.e., mg/kg/day) using 20% dermal absorption rate [default value] should be converted to an equivalent oral dose and combined with this inhalation converted dose (mg/kg/day).

(iii) This combined dose should then be compared to the oral NOELs of 20 mg/kg/ day for Short- and Intermediate-Term exposure and 10.8 mg/kg/day for Long-Term exposures to calculate the Margins of Exposure.

3. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food Sources)

I. Directions for Use (OPPTS GLN 860.1200)

Garbanzo beans : Apply TOUGH ® 3.75 EC herbicide (0.9 lbs. a.i./acre) as a broadcast treatment in 20 to 30 gallons of water per acre using a boom sprayer. A maximum of two treatments may be made per crop with no less than 20 days between treatments. The last treatment (2nd) must be applied no later than 60 days prior to harvest.

ii. Nature of the Residue: Plants, Livestock (OPPTS 860.1300)

No new ^{14}C metabolism studies were submitted with this petition. Studies have been previously submitted (PP#8F3603) for **corn** (MRID 405498-02), **peanuts** (MRID 405498-03), **broccoli** (405498-01), **lactating goats** (MRID # 409179-06), **cows** (MRID # 410224-01), and **laying hens** (MRID # 410458-01). Review of those studies is summarized in the CBTS memo of 12/14/89 (PP#8F3603, E. Haeberer).

Based on those studies, the nature of the residue in plants and ruminants is considered to be adequately understood. The total toxic residue consists of pyridate, its metabolite 6-chloro-3-phenyl-pyridazine -4-ol (aka CL-9673), and conjugates of that metabolite, all expressed as pyridate.

In the poultry study, residues were not identified in tissues or eggs due to the low levels of ^{14}C present. The dosage level was equivalent to 3 ppm in feed.

iii. Residue analytical method (OPPTS GLN 860.1340)

The analytical method used is a total residue procedure. Pyridate, CL-9673, and conjugated CL-9673 are hydrolyzed to CL-9673 and measured as such by UV-HPLC. Pyridate and its main metabolites CL-9673 and conjugated CL-9673 are extracted from plant material by blending with an alkaline solution of ammonium acetate, acetone, and morpholine, whereby pyridate is converted to CL-9673. The extract is evaporated until free from acetone and partitioned between an alkaline solution of ammonium acetate and dichloromethane. The aqueous fraction undergoes an acidic hydrolysis for cleavage of CL-9673 conjugates. The CL-9673 residues are extracted into dichloromethane , which is applied to a "Bond-Elut" Si cartridge. Compound CL-9673 is eluted with a dichloromethane/methanol solution. The eluent is taken to dryness and ammonium acetate buffer is added. After pH adjustment to pH 5.0, 250 microliters of the aqueous phase are injected onto the HPLC. The HPLC uses a column switching technique to transfer the eluent from a dimethylamine column onto a C-18 column where a 15 minutes linear gradient is used to further separate the compounds. Ultraviolet absorbance detection is performed at 280 and 300 nm wavelengths to quantitate the level of CL-9673. The limit of determination is 0.03 ppm.

The method has undergone validation in EPA laboratories (PP#4G3047, L. Propst, 10/5/88) and is suitable to gather residue data and to enforce tolerances. It was sent to FDA for inclusion in PAM II (PP#8F3603, F.

D. Griffith, Jr., 5/2/90). The multiresidue recovery data (MRID# 409179-08) have been sent for inclusion in PAM I (PP#1G3956, F.D. Griffith, Jr., 6/27/91).

Validation data for garbanzo beans matrices fortified (spiked) with CL-9673 have been submitted as follows:

Spike Added, ppm	Percent Recoveries from Garbanzo Beans		Recovery Mean ± Std. Dev.
	beans	beans with pods	
Pyridate, 0.06	92, 92, 83	70, 76, 89	84±9%
Pyridate, 0.6	85, 87, 84	87, 92, 81	86±4%
CL-9673, 0.03	110, 100, 73	80, 83, 70	86±16%
CL-9673, 0.3	83, 82, 78	85, 88, 87	84±4%

iv. Storage Stability (OPPTS GLN 860.1380)

No frozen storage stability data were submitted for garbanzo beans. However, data have previously been submitted (MRID#s 409179-05 and 409179-07; PP#8F3603, E. Haeberer, 12/14/89) on corn, wheat, peanuts, broccoli, alfalfa, rape, and cabbage. Residues of pyridate and CL9673 were stable for up to 2 years in frozen storage, depending on the matrix. Recoveries of 72-96% were reported for wheat grain (at 180 days) and 65-108% for corn foliage (at 101-135 days and 26 months). Garbanzo bean field trial samples were stored frozen for 84 days from harvest to analysis. By translation, adequate storage stability data are available to support the garbanzo beans field trial residue data.

v. Magnitude of the Residue in Water, Fish, and Irrigated Crops (OPPTS GLN 860.1400)

Pyridate is not registered for direct use on potable water or aquatic food and feed crops; therefore, no residue chemistry data are required under these guideline topics.

vi. Food Handling Establishments (OPPTS GLN 860.1460)

Pyridate is not registered for use in food-handling establishments; therefore, no residue chemistry data are required under this guideline topic.

vii. Magnitude of the residue - meat, milk, poultry, and eggs (OPPTS GLN 860.1480)

Since no animal feed items are associated with garbanzo beans, residues will not occur in animal commodities as a result of the proposed use of pyridate in garbanzo beans.

viii. Magnitude of the residue - crop field trials (OPPTS GLN 860.1480)

Field trials were conducted in 4 states (CA, ID, OR, WA) in 1993 on garbanzo bean plants (MRID #'s 439232-00 and 439232-01). The number of field trials and geographical representation are adequate.

Field sites were sprayed with Tough 3.75EC at rates of 0.9 lbs ai/A (1X the proposed label rate) or 1.8 lbs ai/A by ground boom or backpack sprayer, using 25-26 gals water/A. The first application was made at early post emergence of weeds (2-6 leaf stage) followed by a second application 20 ± 2 days later. Plot size for each of the treatments were 10-30 feet wide by 50-100 feet long. Buffer zones between treated and untreated fields were 62-100 feet.

Bean and bean with pod samples (3 replicates) were harvested at normal crop maturity (i.e., 60-64 days after the second treatment) from both control and treated plots and stored frozen until analysis by Agrolinz Agrarchemikalien Ges.m.b.H., Leonding, Austria. (performing laboratory) for the total regulable residue.

The results are shown below (as ppm CL9673).

Table 10. Pyridate Residues on Garbanzo Beans (Chickpeas)

Trial Number/Matrix	Rate lb ai/acre)	PHI (days)	CL-9673 ppm*	MAXIMUM (ppm)*
3866.93-ID03				
bean	0.0 (UTC)	60	0.030	
bean	0.9	60	0.057	0.057
bean	0.9	60	0.030	
bean	1.8	60	<0.030	<0.030
bean	1.8	60	<0.030	
3866.93-OR28				
bean	0.0 (UTC)	64	<0.030**	
bean	0.9	64	<0.030	
Bean	0.9	64	<0.030	
bean	0.9	64	<0.030	<0.030
bean	0.9	64	<0.030	
bean	1.8	64	<0.030	
bean	1.8	64	<0.030	<0.030
bean	1.8	64	<0.030	
bean	1.8	64	<0.030	
beans with hulls	0.0 (UTC)	64	<0.030	
beans with hulls	0.9	64	<0.030	
beans with hulls	0.9	64	<0.030	<0.030
beans with hulls	0.9	64	<0.030	
beans with hulls	0.9	64	<0.030	
beans with hulls	1.8	64	<0.030	
beans with hulls	1.8	64	<0.030	<0.030
beans with hulls	1.8	64	<0.030	
beans with hulls	1.8	64	<0.030	

Trial Number/Matrix	Rate lb ai/acre)	PHI (days)	CL-9673 ppm*	MAXIMUM (ppm)*
3866.93-WA31				
bean	1.8	61	<0.030	< 0.030
bean	1.8	61	<0.030	
3866.93-CA58				
bean	0.0 (UTC)	64	<0.030***	
bean	0.9	64	<0.030	
bean	0.9	64	<0.030	<0.030
bean	0.9	64	<0.030	
bean	0.9	64	<0.030	
bean	1.8	64	<0.030****	
bean	1.8	64	<0.030	<0.030
bean	1.8	64	<0.030	
bean	1.8	64	<0.030	

* Values are ppm pyridate, CL-9673 and hydrolyzable CL-9673 conjugates in sum, expressed as CL-9673.

** Probably due to contamination in the laboratory, 1.2 ppm CL-9673 was initially found in the control sample. The control sample was reanalyzed twice and no residues (<0.030 ppm CL-9673) were found.

*** Probably due to contamination in the laboratory, 0.39 ppm CL-9673 was initially found in the control sample. The control sample was reanalyzed twice and no residues (<0.030 ppm CL-9673) were found.

**** Probably due to contamination in the laboratory, 1.5 ppm CL-9673 was initially found in this sample. The sample was reanalyzed and no residues (<0.030 ppm CL-9673) were found.

The maximum residue (pyridate, CL-9673, and hydrolyzable CL-9673 in sum, expressed as CL-9673) recovered in any bean sample from garbanzo plants treated twice at the proposed label rate of 0.9 lbs ai/A was 0.057 ppm. The maximum pyridate residue recovered in bean plus hull samples from garbanzo plants treated twice at the proposed label rate of 0.9 lbs ai/A was <0.030 ppm.

The maximum residue (pyridate, CL-9673, and hydrolyzable CL-9673 in sum, expressed as CL-9673) recovered in any bean sample from garbanzo plants treated twice at the proposed label rate of 1.8 lbs ai/A was <0.030 ppm. The maximum pyridate residue recovered in bean plus hull samples from garbanzo plants treated twice at the proposed label rate of 1.8 lbs ai/A was <0.030 ppm. Therefore, the combined residues of pyridate [O-(6-chloro-3-phenyl-4-pyridazinyl)-S-octyl-carbonothioate], the metabolite 6-chloro-3-phenyl-pyridazine-4-ol and conjugates of 6-chloro-3-phenyl-pyridazine-4-ol, expressed as pyridate resulting from the proposed use will not exceed 0.1 ppm in garbanzo beans.

None of these submitted field trials include the addition of an adjuvant or surfactant to the spray mix, as the proposed directions for use allow. HED cannot conclude that the presence of such additives would not result

in over tolerance residues. **To address this deficiency, revise Section B to read as follows: "Adjuvants (non-ionic surfactants, crop oil or liquid fertilizer) are prohibited from use with TOUGH 3.75 EC when used on garbanzo beans".** (Note: Section A prohibits use of adjuvants with TOUGH 3.75 EC for use on peanuts. The same restriction should be extended to garbanzo beans).

ix. Magnitude of the Residue in Processed Food/Feed (OPPTS GLN 860.1520)

There are no processed commodities associated with garbanzo beans; thus, a processing study is not needed.

x. Confined Accumulation in Rotational Crops (OPPTS GLN 860.1850)

A confined accumulation in rotational crops study with pyridate has previously been submitted and reviewed by EFGWB/EFED. The study was judged to be acceptable to satisfy the data requirements of GRN 65-1 (Richard J. Mahler, 3/16/90). To summarize, confined rotational crop data using ^{14}C-pyridate at an application rate of 1.8 kg/ha showed no detectable uptake (<0.01 ppm) of residues (pyridate, CL-9673, or CL-9673-OMe) by lettuce, carrots, or barley after a rotational interval of 1 and 2 months. These findings were supported by data showing the rapid metabolism in soil of pyridate residues.

xi. Field Accumulation in Rotational Crops (OPPTS GLN 860. 1900)

No field rotational crop study (GRN 65-2) was required. No label restrictions are needed.

xii. Reduction of Residues - Anticipated Residues

Not applicable.

xiii. International Harmonization of Tolerances

There are no CODEX, Canadian, or Mexican tolerances for pyridate residues on garbanzo beans.

b. Dietary Exposure (Drinking Water Source)

Based on information provided by EFED (John Simons/Environmental Risk Branch 2, memo dated 11/21/97), pyridate hydrolyzes rapidly in terrestrial and aquatic environments to the degradate CL-9673, with half-lives usually ≤ 3 days. Although pyridate is also rapidly hydrolyzed under anaerobic soil conditions to CL-9673, CL-9673 is persistent and undergoes very little degradation with half lives from 330 to 630 days in anaerobic soil conditions. Aerobic half lives of CL-9673 are about 10-30 weeks in soils (incorrectly given as 10-30 days in the EPA one-liner database). CL-9673 is rapidly degraded under the influence of light as indicated by the 14 day half life in water and 16 day half life in soil. In general, pyridate and its primary degradate CL-9673, will not persist in aerobic conditions, while CL-9673 will persist in anaerobic conditions. It is also mobile, with computed K_{oc} values for three soils ranging from 3 to 86.5. Some leaching to ground water is predicted from these fate characteristics.

i. Ground Water

Although pyridate does not possess the environmental fate parameters associated with a compound that could leach to ground water, the fate parameters of its degradate CL-9673 seem to indicate that it has the potential to leach to ground water (K_d of 0.3 - 3.5), especially in soils of low organic matter. In unusual conditions such as flooding, where anaerobic conditions exist in the top soil layers for up to 60 days, CL-9673 could persist and possibly leach to ground water or run off to surface water.

Pyridate is not listed in EPA Pesticides in Ground Water Database, nor is there an EPA Maximum Contaminant Level or health advisory.

The drinking water exposure from the ground water screening model, SCI-GROW, yields a peak Estimated Environmental Concentration (EEC) of 5 ppb in ground water. There may be exceptional circumstances under which ground water concentration could exceed the SCI-GROW estimates. However, such exceptions should be quite rare since the SCI-GROW model is based exclusively on maximum ground water concentrations from studies conducted at sites and under conditions which are most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW are based on the largest 90-day average recorded during the sampling period. The concentration of 5 ppb can be considered as both the acute and chronic values.

ii. Surface Water

The GENEEC model was used to estimate surface water concentrations for pyridate resulting from its use on garbanzo beans. The modeling results indicate that pyridate has the potential to move into surface waters, especially during times of unusually heavy rainfall. The peak GENEEC EEC of pyridate in surface water is 97 ppb, and the average 56-day EEC is 75 ppb. This estimate is based on a maximum application rate of 0.9 lbs ai/acre. The GENEEC values represent upper-bound estimates of the concentrations that might be found in surface water due to pyridate use.

c. Dietary Risk Assessment and Characterization

I. Chronic Risk

The chronic dietary exposure analysis from food sources was conducted using the reference dose (RfD) of 0.11 mg/kg/day. The RfD is based on the NOEL of 10.8 mg/kg/day in male rats from the Chronic Toxicity/Carcinogenicity study in rats (MRIDs 00137289, 00137290, 00138638), and an uncertainty factor of 100 applicable to all population subgroups.

In conducting this chronic dietary risk assessment, EPA has made very conservative assumptions: 100% of garbanzo beans (chickpeas) and all other commodities having pyridate tolerances will contain pyridate residues and those residues will be at the level of the established tolerance. This results in an overestimate of human dietary exposure. Thus, in making a safety determination for this tolerance, EPA is taking into account this conservative exposure assessment.

The existing pyridate tolerances (published, pending, and including the necessary Section 18 tolerances) result in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the following percentages of the RfD:

Population Subgroup	%RfD
U.S. Population (48 states)	0.014
Nursing Infants (<1 year old)	**0.009**
Non-Nursing Infants	**0.028**

(<1 year old)	
Children (1-6 years old)	**0.033**
Children (7-12 years old)	**0.025**
Southern Region	0.016
Western Region	0.015
Hispanics	0.018
Non-Hispanic Others	0.020
Males (13-19 years old)	0.015

The subgroups listed above are: (1) the U.S. population (48 states); (2) those for infants and children; and (3) the other subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 states).

ii. Carcinogenic Risk

The carcinogenic potential of pyridate has not been evaluated. However, the DERs for the mouse and rat oncogenicity studies indicate that pyridate is negative in both species for carcinogenic effects. Thus, a cancer risk assessment is not required.

iii. Acute Dietary Risk

As previously stated, the endpoint selected by the HAZID Committee (10/21/97) for assessment of acute dietary risk is 20 mg/kg/day (NOEL), based on a 90-day feeding study on dogs (MRID 40101604). Thus, this risk assessment is required for all population subgroups.

This acute dietary (food) risk assessment used the Theoretical Maximum Residue Contribution (TMRC). Resulting exposure values and MOEs (MOE = Acute Endpoint ÷ Exposure) are shown below.

Population Subgroup	NOEL (mg/kg/day)	High-End Exposure (mg/kg/day)	MOE
U.S. Population (48 states)	20	0.00018	100000
Infants (< 1 yr)	20	0.0005	40000
Children (1-6 yrs)	20	0.0003	70000
Females (13+ yrs)	20	0.00012	170000
Males (13+ yrs)	20	0.00012	170000

iv. Drinking Water Risk (Acute and Chronic)

HED followed OPP's Interim Approach for Addressing Drinking Water Exposure in Tolerance Decision making issued on 11/17/97. Thus, the GENEEC model and the SCI-GROW model were run to produce estimates of pyridate concentrations in surface and ground water respectively. The primary use of these

models is to provide a coarse screen for sorting out pesticides for which OPP has a high degree of confidence that the true levels of the pesticide in drinking water will be less than the human health drinking water levels of concern (DWLOCs). A human health DWLOC is the concentration of a pesticide in drinking water which would result in unacceptable aggregate risk, after having already factored in all food exposures and other non-occupational exposures for which OPP has reliable data.

$$DWLOC_{acute} = \frac{[\text{water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg}/\mu\text{g}]}$$

$$\text{where water exposure (mg/kg/day)} = \frac{\text{NOEL (mg/kg/day)}}{\text{MOE}} - \text{food exposure (mg/kg/day)}$$

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg}/\mu\text{g}]}$$

where chronic water exposure (mg/kg/day) = [RfD - (chronic food + residential exposure) (mg/kg/day)]

The $DWLOC_{acute}$ is the concentration in drinking water as a part of the aggregate acute exposure that results in an acceptable MOE. The $DWLOC_{chronic}$ is the concentration in drinking water as part of the aggregate chronic exposure that results in a negligible cancer risk. The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male), 60 kg/2L (adult female), and 10 kg/1L (child).

The results are summarized below:

Population Subgroup	Acute Scenario[1]				Chronic Scenario[2]			
	NOEL mg/kg/day	DWLOC μg/L	Ground Water SCI-GROW EEC in μg/L	Surface Water GENEEC EEC in μg/L	RfD mg/kg/day	DWLOC	SCI-GROW EEC in μ/L	GENEEC[3] EEC in μ/L
Male (13 yrs +)	20	7000	5	97	0.11	3850	5	25
Female (13 yrs +)	20	7000	5	97	0.11	3300	5	25
Child (1-6 yrs)	20	7000	5	97	0.11	1100	5	25

1 Assuming an MOE of 100.
2 DRES TMRCs in mg/kg/day: male (13 yrs +) = 0.000017, female (13 yrs +) = 0.000014, child (1-6 yrs) = 0.000036
3 The average EEC for surface water of 75 ppb÷3 = 25 ppb.

As shown above, the calculated drinking water levels of concern (DWLOCs) for acute exposure to pyridate in surface and ground water are 7000 μg/L for all 3 population subgroups. For chronic (non-cancer) exposure

to pyridate in surface and ground water, the drinking water levels of concern are 3850 μg/L for males (13 yrs+), 3300 μg/L for females (13 yrs+) and 1100 μg/L for children (1-6 yrs). To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DRES analysis) was subtracted from the ratio of the acute NOEL (used for acute dietary assessments) to the "acceptable" for aggregate exposure to obtain the acceptable acute exposure to pyridate in drinking water. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DRES) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to pyridate in drinking water. DWLOCs were then calculated using default body weights and drinking consumption figures.

Estimated maximum concentrations of pyridate in surface and ground water are 97 and 5 ppb respectively. Estimated average concentrations of pyridate in surface and ground water are 25 (after adjustment) and 5 ppb respectively. The maximum estimated concentrations of pyridate in surface and ground water are less than OPP's levels of concern for pyridate in drinking water as a contribution to acute aggregate exposure. The estimated average concentrations of pyridate in surface and ground water are less than OPP's level of concern for pyridate in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of pyridate in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

4. Occupational and Residential Exposure and Risk Assessment/Characterization

As previously stated, the HAZARD ID Committee determined (10/21/97) that occupational and residential exposure assessments (namely short-, intermediate-, and long-term dermal) were required.

a. Occupational and Residential Exposure

Pyridate is not currently registered for any residential uses; therefore, residential exposure is not required.

I. Summary of Use Patterns and Formulations: Occupational

The information in Table 11, below, is taken from the label for Tough 3.75 EC and other sources as cited.

Table 11. Registration Request for Use of Tough 3.75 EC in/on garbanzo beans (Chick peas).

Factors	Comments
Crop to be treated	Garbanzo beans (chick peas)
Pests	Post emergent control of broadleaf weeds.
Application methods	Aerial and Groundboom application.
Maximum application rate	Tough 3.75 EC: 0.9 lbs. ai/A **(Do not apply more than 1.8 (3 pints) lbs ai/A per season).**
Maximum number of applications	Two treatments may be made per crop with no less than 20 days between treatments. The last treatment (2nd) must be applied no later than 60 days prior to harvest.

Percent Absorption	A 20% Dermal Absorption value is applicable for short and intermediate term occupational exposure (toxicology endpoints for these scenarios are derived from an oral developmental toxicity study).
Average Acreage of Application per Day	**Aerial** - 350, and **Ground boom** - 80 acres[1]
Manufacturer	Sandoz Agro, Inc.

[1] The estimate of maximum acreage used in this assessment of worker exposure is representative of the maximum standard acreage for Aerial and Ground boom on garbanzo beans.

Acute toxicity endpoints are established for the active ingredient for short-term, intermediate-term, and chronic occupational or residential exposure. The short- and intermediate- term endpoints are derived from a 90-Day feeding study in dogs. The NOEL for both short- and intermediate-term exposures is 20 mg/kg/day The chronic endpoint is derived from a combined chronic toxicity/carcinogenicity study in rats; the NOEL for the chronic exposure is 10.8 mg/kg/day.

Risk assessments are required for short-term, intermediate-term, and chronic exposure, where appropriate. This active ingredient will not be used over several months; hence, a chronic exposure assessment is not required.

The Hazard I. D. Committee generally does not consider workers to be at risk from inhalation exposure due to the low toxicity of the chemical (Toxicity Category IV), provided there is no potential for a high exposure. Compared to dermal exposure, inhalation exposure is considered very low (less than 6%). The vapor pressure of pyridate is 1.01×10^{-7} mm Hg, which is an indication of the herbicide's volatility. Pyridate's volatility is minimal, and not a concern. Based on the above information, EPA concludes that inhalation exposure is not a concern .

TYPE OF TOXICITY	**TOXICITY CATEGORY**	
	Active ingredient	**Tough 3.75 EC (43.5% ai)**
Acute Oral	III	III
Acute Dermal	III	III
Acute Inhalation	IV	IV
Primary Eye	IV	III
Primary Dermal	III	III
Dermal Sensitization	A strong sensitizer	A strong sensitizer

ii. Handler Exposures and Assumptions

HED's exposure assessment is based on the assumptions in Table 12.

Table 12. Assumptions for Worker Exposure Assessments

Factors	Quantities/Units
Applicator body weight	70 kg
Mixer/loader body weight	70 kg
Application rate (Aerial and Groundboom)	0.9 lb ai/A (Tough 3.75 EC)
Acres treated per day (Aerial) Acres treated per day (Groundboom)	350 acres 80 acres[1]
Applicator unit exposure from PHED (Aerial application; liquid; closed cab; with long-pants, long-sleeved shirt, and no gloves).	5.0 µg/lb ai handled[2]
Applicator unit exposure from PHED (Groundboom application; liquid; open cab; with long-pants, long-sleeved shirt, and gloves).	14.0 µg/lb ai handled[2]
Mixer/loader unit exposure from the Pesticide Handlers Exposure Database (PHED), (In support of Aerial and Groundboom application; liquid; open mixing; with long pants, long-sleeved shirt, and gloves).	23.0 µg/lb ai handled[3]
Mixer/loader/Applicator unit exposure from the Pesticide Handlers Exposure Database (PHED), (In support of Groundboom application; liquid; open mixing; with long pants, long-sleeved shirt, and gloves).	48.0 µg/lb ai handled[4]
Personal protective equipment (PPE), per label.	**For Tough 3.75 EC:** Long-sleeved shirt and long pants; chemical-resistant gloves and protective eyeware; shoes plus socks.

[1] Standard assumptions of the acreage treated per day given the application method and ground speed.
[2] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): for applicators (Aerial, pg 36; Groundboom, pg 27), liquid, closed cab (aerial)/open cab (groundboom), long pants, long sleeves, no gloves (aerial)/gloves (groundboom).
[3] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): page 19, for mixer/loaders, Aerial & Groundboom, liquid, open mixing, with, long pants, long sleeves, gloves.
[4] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): for mixer/loader/ applicators (Groundboom, pg 45), liquid, open cab, long pants, long sleeves, gloves.

iii. Post-Application Exposures & Assumptions - Occupational

During the harvesting of garbanzo beans (chick peas), which is considered to be a low exposure activity due to mechanical harvesting (similar to dry beans), there is not a potential for significant post-application exposure to the harvesters.

iv. Mixer/Loader/Application Exposure Assessment

Table 13, below, summarizes the HED/HED's estimates for total worker exposure for applicators and mixer/loaders in the proposed use of pyridate on garbanzo beans (chick peas). These estimates are based on the assumptions outlined in Table 12.

Table 13. Worker Exposure to Tough 3.75 EC herbicide

Job Function	Average Dermal Daily Dose for Tough 3.75 EC mg ai/kg bw/day	Dermal Short & Intermediate-Term MOE
Applicators	Aerial - 0.0225 Groundboom -0.0144	Aerial - 889 Groundboom - 1,389
Mixer/loaders	Aerial - 0.1035 Groundboom -0.0237	Aerial - 193 Groundboom - 844
Mixer/Loader &Applicator	Groundboom (only) - 0.0494	405

MOE = NOEL/ADD (where NOEL = 20 mg/kg/day)

The exposure estimates in Table 7 are based on treatment of 350 acres per day by aerial and 80 acres per day by ground boom.

The following calculations were used to determine the expected worker exposures resulting from the handling and application of pyridate (Tough 3.75 EC) to garbanzo beans (chick peas):

Applicators:

Aerial

$$0.9\ lbs.\ ai\ applied/acre \times 350\ of\ acres\ treated/day = 315\ lbs\ ai/day$$

$$5.0\ \mu g/lb\ ai\ handled\ (PHED,\ Version\ 1.1) \times 315\ lbs\ ai/day = 1575\ \mu g\ ai/day$$

$$\frac{1575\ \mu g\ ai/day}{70\ kg\ bw} = 22.5\ \mu g\ ai/kg\ bw/day$$

$$\frac{22.5\ \mu g\ ai/kg\ bw/day}{1000\ \mu g} = 0.0225\ mg\ ai/kg\ bw/day$$

Groundboom

$$0.9\ lbs.\ ai\ applied/acre \times 80\ of\ acres\ treated/day = 72\ lbs\ ai/day$$

$$14.0\ \mu g/lb\ ai\ handled\ (PHED,\ Version\ 1.1) \times 72\ lbs\ ai/day = 1008\ \mu g\ ai/day$$

$$\frac{1008\ \mu g\ ai/day}{70\ kg\ bw} = 14.4\ \mu g\ ai/kg\ bw/day$$

$$\frac{14.4\ \mu g\ ai/kg\ bw/day}{1000\ \mu g} = 0.0144\ mg\ ai/kg\ bw/day$$

Mixer/Loaders:

Aerial

0.9 *lbs. ai applied/acre* × 350 *of acres treated/day* = 315 *lbs ai/day*

23.0 µg/*lb ai handled* (*PHED, Version* 1.1) × 315 *lbs ai/day* = 7245.0 µg *ai/day*

$$\frac{7245.0\ \mu g\ ai/day}{70\ kg\ bw} = 103.5\ \mu g\ ai/kg\ bw/day$$

$$\frac{103.5\ \mu g\ ai/kg\ bw/day}{1000\ \mu g} = 0.1035\ mg\ ai/kg\ bw/day$$

Groundboom

0.9 *lbs. ai applied/acre* × 80 *of acres treated/day* = 72 *lbs ai/day*

23.0 µg/*lb ai handled* (*PHED, Version* 1.1) × 72 *lbs ai/day* = 1656.0 µg *ai/day*

$$\frac{1656.0\ \mu g\ ai/day}{70\ kg\ bw} = 23.7\ \mu g\ ai/kg\ bw/day$$

$$\frac{23.7\ \mu g\ ai/kg\ bw/day}{1000\ \mu g} = 0.0237\ mg\ ai/kg\ bw/day$$

Mixer/Loader/Applicator

Groundboom

0.9 *lbs. ai applied/acre* × 80 *of acres treated/day* = 72 *lbs ai/day*

48.0 µg/*lb ai handled* (*PHED, Version* 1.1) × 72 *lbs ai/day* = 3456.0 µg *ai/day*

$$\frac{3456.0\ \mu g\ ai/day}{70\ kg\ bw} = 49.4\ \mu g\ ai/kg\ bw/day$$

$$\frac{49.4\ \mu g\ ai/kg\ bw/day}{1000\ \mu g} = 0.0494\ mg\ ai/kg\ bw/day$$

v. Post-Application Exposure Assessment

The petitioner did not provide post-application exposure sampling data.

b. Occupational and Residential Risk Assessment/Characterization

I. Risk from Dermal and Inhalation Exposures

The Agency does not generally have an occupational or residential concern unless MOEs are below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for interspecies extrapolation and intraspecies variability. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. The additional 10X is not necessary for pyridate (per Hazard I.D. Comm.) due to no

increased sensitivity to infants and children; therefore, HED's level of concern for pyridate are for MOEs that are below 100.

Chronic exposure is not expected for use of pyridate on garbanzo beans (chick peas); hence, a chronic risk assessment will not be done.

Table 13 summarizes HED's estimates for MOEs for total worker exposure for Applicators and Mixer/Loaders for the proposed use of pyridate on garbanzo beans. These estimates are based on the assumptions outlined in sections 4.a.ii. and 4.a.iii. above.

Both short- and intermediate- term occupational exposures are likely for the following reason: An expected average of 20,000-30,000 acres per year (IR-4 Study 03866, pg. 25, proposed use, within the United States, data of 1994) of garbanzo beans, within the Pacific Northwest of the United States, are treated by aerial and/or groundboom applications. (If done entirely by the aerial method, it would take 57-85.7 days/year; if done entirely by the groundboom method, it would take 250-375 days/year.) However, since all MOEs reported are higher than 100, HED anticipates the risk to the worker will be minimal for these exposure scenarios.

The personal protective equipment (PPE) required by the label for Tough 3.75 EC is summarized in Table 12. The PPE requirements as represented on the label for Tough 3.75 EC are in compliance with the Worker Protection Standard.

Based on the assumptions within this risk assessment, the following restrictions should be incorporated in the registrant's label: 1) this herbicide is not for residential use; 2) harvesting will be done mechanically only; and 3) aerial application must be done with an enclosed cockpit.

ii. Risk From Post-Application Exposures

Post-application is not likely to be a problem due to the low toxicity category of pyridate (Tox. Cat. IV) and the use of mechanical harvesting. However, there are other activities such as scouting, moving irrigation pipes, etc., that could pose an exposure concern because pyridate can be added anytime after post-emergence of the garbanzo bean plant. Thus, the petitioner is required to submit dislodgeable foliar residue and post-application re-entry generic data as soon as it becomes available. (Note: the petitioner is a member of the Agriculture Re-Entry Task Force which is currently engaged in collecting these data). These data will allow and effective and efficient occupational risk assessment/characterization to be done based on actual sampling results.

iii. Restricted Entry Interval

Based on the Tox Category, the appropriate REI is 12 hours. The Tough 3.75 EC label is in compliance with the REI of 12 hours.

iv. Incident Reports

There were no incidents noted in the U.S. on the REFS database system concerning pyridate.

c. Statement of the adequacy of the residential exposure database to assess infants' and children's exposures

The registration for use of pyridate on garbanzo beans (chick peas) should not result in residential exposure, because it is only applied to commercial crops. The REFS database system was reviewed, and indicated no previous residential uses for pyridate.

5. Aggregate Exposure and Risk Assessment Characterization

a. Acute Aggregate Exposure and Risk

From the acute dietary (food only) risk assessment, the following high end exposure estimates were calculated: 0.00018 mg/kg/day for the general U.S population; 0.00012 mg/kg/day for males (13+ yrs); 0.00012 mg/kg/day for females (13+ years); 0.0005 mg/kg/day for infants (<1 yr); 0.0003 mg/kg/day for children (1-6 yrs). These exposures yield dietary (food only) MOEs ranging from 40000 to 170000 (see Section 3.c.*iii.*) for these population subgroups. The maximum estimated concentrations of pyridate in surface and ground water are less than OPP's levels of concern for pyridate in drinking water as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of pyridate in drinking water do not contribute significantly to the aggregate acute human health risk at the present time when considering the present uses and the uses proposed by this action.

OPP bases this determination on a comparison of estimated concentrations of pyridate in surface and ground water to levels of concern for pyridate in drinking water. The estimates of pyridate in surface and ground water are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with the pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impact of pyridate in drinking water as part of the aggregate acute risk assessment process.

b. Short- and Intermediate-term Aggregate Exposure and Risk

Pyridate is not currently registered for any residential uses. Therefore, no residential exposure (short- or intermediate-term) is anticipated and a short- and intermediate-term aggregate risk assessment is not required.

c. Chronic Aggregate Exposure and Risk.

For the U.S. population, 0.014% of the RfD is occupied by dietary (food) exposure. Because pyridate has no residential uses, no chronic residential exposure is anticipated. The estimated average concentrations of pyridate in surface and ground water are less than OPP's level of concern for pyridate in drinking water as a contribution to chronic aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of pyridate in drinking water do not contribute significantly to the aggregate chronic human health risk at the present time when considering the present uses and uses proposed by this action.

OPP bases this determination on a comparison of estimated concentrations of pyridate in surface and ground water to levels of concern for pyridate in drinking water. The estimates of pyridate in surface and ground water are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with the pesticide's uses, levels of concern in

drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impact of pyridate in drinking water as part of the aggregate chronic risk assessment process.

6. Other Food Quality Protection Act Considerations

a. Cumulative Risk from Exposure to Substances with a Common Mechanism of Toxicity

Pyridate is a member of the pyridazinone class of herbicides. Other chemicals in this class are pyrazon and norflurazon.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether pyridate has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of these tolerance actions, therefore, EPA has not assumed that pyridate has a common mechanism of toxicity with other substances.

b. Endocrine Disrupter Effects

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

c. Determination of Safety (U.S. Population, Infants, and Children)

Pyridate has been classified as a Group E chemical, with no evidence of carcinogenicity for humans in two acceptable animal studies. Thus, a cancer risk assessment is not required.

Occupational exposure (short- and intermediate-term) estimates do not exceed HED's level of concern. Pyridate will not be used over several months; thus, chronic exposure assessment is not required. Pyridate does not have residential uses; therefore, no residential risk assessment is required.

Acute and chronic aggregate dietary (food + water) risk estimates do not exceed HED's level of concern. Establishment of the proposed tolerance should not pose an unacceptable aggregate risk to infants, children, or adults.

Attachment 1: DRES Run: Acute and Chronic: M. Ottley/B. Steinwand, 11/18/97

cc with attachment: M. Lamont, W. Dykstra, J. Cruz , RAB1 File
cc without attachment: OREB File, Caswell File
RDI: RAB1: 12/19/97

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Chemical:	**Carbonothioic acid, O-(6-chloro-3-phenyl**
PC Code:	**128834**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**12/22/97**
File ID:	**DPD223398**
Accession Number:	**412-02-0280**

HED Records Reference Center
04/10/2002